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Phytochemicals in cancer prevention: Current advances, molecular mechanisms and future perspectives

Pallab Ray
Assistant Professor, Department of Zoology, Ananda Mohan Collge affiliated to University of Calcutta, Raja Rammohan Sarani, Kolkata, West Bengal, India
Corresponding Author: Pallab Ray
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Abstract
Cancer remains one of the leading causes of global morbidity and mortality, creating an urgent need for effective, safe, and affordable preventive strategies. Dietary phytochemicals have emerged as promising chemopreventive agents because of their structural diversity and ability to modulate multiple molecular pathways involved in carcinogenesis. This review critically synthesizes current evidence on the role of phytochemicals in cancer prevention by examining their classification, dietary sources, molecular mechanisms of action, preclinical findings, clinical evidence, pharmacological limitations, and emerging translational strategies. The review encompasses approximately 120 peer-reviewed publications published between 2010 and 2025, providing a comprehensive overview of advances in this rapidly evolving field. Major classes of phytochemicals, including polyphenols, flavonoids, alkaloids, terpenoids, organosulfur compounds, and carotenoids, are discussed with emphasis on their ability to regulate oxidative stress through Nrf2 activation, suppress NF-κB-mediated inflammatory signalling, induce cell cycle arrest, promote apoptosis and autophagy, modulate epigenetic regulation, inhibit angiogenesis, reduce extracellular matrix (ECM) remodelling, and enhance immune surveillance. Despite encouraging preclinical evidence, their clinical translation remains constrained by poor aqueous solubility, limited bioavailability, rapid metabolism, physicochemical instability, and considerable inter-individual pharmacokinetic variability associated with gut microbiota composition and genetic polymorphisms. Recent advances in nanotechnology-based delivery systems, multi-omics approaches, artificial intelligence-assisted drug discovery, and precision nutrition offer promising strategies to overcome these limitations and improve translational potential. Collectively, current evidence indicates that phytochemicals represent valuable complementary agents for cancer prevention; however, robust biomarker-driven clinical trials and standardized formulations are required to establish their long-term clinical efficacy and facilitate their integration into evidence-based precision oncology.

Keywords: Apoptosis, bioavailability, chemoprevention, epigenetic dietetics, nanomedicine, secondary metabolites

Introduction

1. Global Burden of Cancer and the Need for Preventive Strategies

Malignant neoplasms remain one of the leading causes of morbidity and mortality worldwide and represent a major public health challenge of the twenty-first century. According to the Global Cancer Observatory (GLOBOCAN 2022) [12], an estimated 20 million new cancer cases and 9.7 million cancer-related deaths occurred globally in 2022 [12], and the annual incidence is projected to exceed 35 million new cases by 2050, representing an increase of approximately 77% compared with current estimates [1]. Despite remarkable advances in targeted therapies, precision immunotherapy, molecular diagnostics, and minimally invasive surgical techniques, the prognosis for many advanced-stage malignancies remains suboptimal, with substantial disease recurrence, therapeutic resistance, and mortality. Furthermore, the escalating economic burden of cancer, treatment-associated toxicities, and the widespread emergence of multidrug resistance underscore the urgent need for complementary preventive strategies that can reduce cancer incidence before disease onset.

Such a paradigm shift to preventive oncology is a must. Cancer prevention is the most cost effective, long-term and sustainable option to reduce the global burden of cancer. The epidemiological evidence indicates that roughly 30–50% of all cancers may be prevented by changing external risk factors [2]. Of these, chronic exposure to environmental carcinogens and sedentary lifestyle, combined with poor dietary habits, are among the major factors that are involved in tumor initiation and promotion. Making lifestyle changes, especially the shift to calorie optimized, nutrient dense diets with a greater focus on plant-based foods, has been shown to have significant impact on reducing the relative risk of developing epithelial and hematological malignancies [3]. It is critical to understand the molecular components that underlie these dietary interventions in order to develop comprehensive chemopreventive strategies.

2. Phytochemicals as Emerging Chemopreventive Agents

Phytochemicals are the non-nutritive, structurally varied secondary metabolites produced by plants as protective compounds against attack by mechanical injury, pathogens and environmental stress [4]. They are not directly involved in the fundamental metabolic activities of plant growth or reproduction, but they are compounds of great therapeutic value in human physiology. These bioactive compounds found in plants are potent potential chemopreventive agents that could act at various stages of carcinogenesis, such as initiation, promotion, and progression, in the context of oncology.

Dietary phytochemicals are able to affect several targets within the cells without causing a systemic toxicity, which is why they are effective at disease prevention. These compounds do not have one mechanism but rather multiple cell responses [5]. They may be blocking agents to keep carcinogens away from or from reacting with critical target organs, or they may be suppressing agents to inhibit the malignant transformation of pre-neoplastic cells. At the cellular level, these molecules have subtle effects on endogenous physiological processes, such as restoring redox homeostasis, downregulating pro-inflammatory signaling cascades, arresting cell cycle and activating intrinsic apoptotic pathways in aberrant cells [6]. Owing to their ability to simultaneously regulate multiple interconnected molecular pathways, phytochemicals have considerable potential to interrupt the early stages of carcinogenesis by preventing cellular transformation, suppressing tumour promotion, and delaying disease progression.

3. Aim and Scope of the Review

In light of the growing amount of literature on plant-derived compounds, a detailed study of their diverse applications in oncology is highly recommended. Although numerous reviews have examined the anticancer properties of phytochemicals, most have focused primarily on individual compounds, specific signalling pathways, or isolated therapeutic mechanisms. Relatively few reviews critically integrate recent advances spanning molecular mechanisms, preclinical evidence, clinical investigations, pharmacological limitations, nanotechnology-based delivery systems, multi-omics approaches, and artificial intelligence-driven strategies within a single comprehensive framework. Moreover, many existing reviews provide descriptive summaries while offering limited critical evaluation of the major barriers hindering successful clinical translation, including poor bioavailability, pharmacokinetic variability, formulation challenges, and inconsistent clinical outcomes. Addressing these gaps is essential for identifying future research priorities and facilitating the development of evidence-based phytochemical interventions for cancer prevention.

The primary objective of this review is to critically evaluate contemporary evidence regarding the role of dietary phytochemicals in cancer prevention by integrating recent findings from molecular biology, preclinical investigations, clinical studies, pharmacology, nanomedicine, and precision oncology. It covers comprehensive classification of the main families of phytochemicals, a survey of their occurrence in the diet and extensive mechanistic studies of the effects of these compounds on the major cellular signaling networks.

It is important to bridge the gap between basic *in vitro* observations and the actual clinical outcome, to move the field forward. This review concentrates on the exact molecular targets that these agents regulate, and at the same time covers the existing pharmacological shortcomings, including the bioavailability and metabolic stability in the systemic circulation. This article draws from these different points of view to offer a balanced view of the issues and options of taking research results out of the laboratory and into a viable public health program. The general concept of phytochemical mediated cancer prevention, from dietary intake to modulation of molecular pathways and cancer prevention outcomes is shown in the figure (Figure 1).

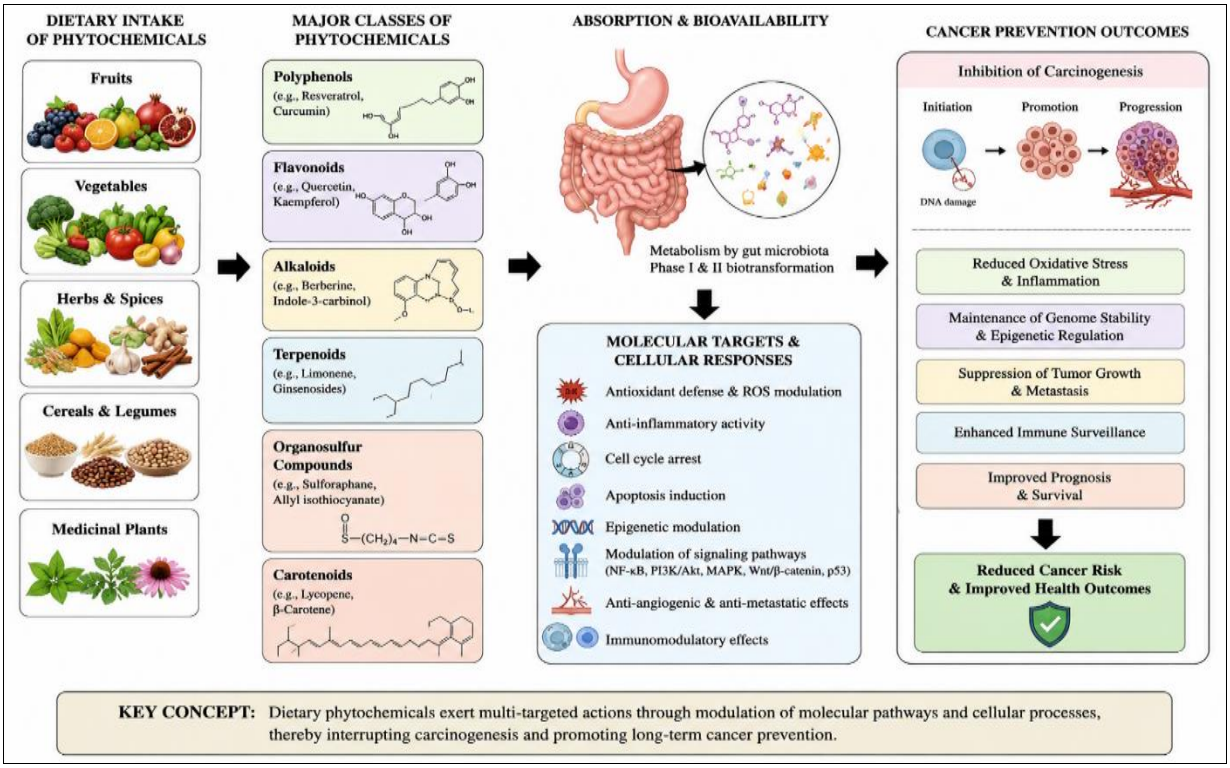

Fig 1: Overview of phytochemical-mediated cancer prevention illustrating the progression from dietary intake and gastrointestinal bioavailability to modulation of intracellular molecular targets, regulation of cellular responses, and subsequent cancer prevention outcomes. Representative phytochemicals regulate oxidative stress, inflammation, cell cycle progression, apoptosis, autophagy, epigenetic modifications, angiogenesis, and immune surveillance, collectively contributing to the prevention of tumour initiation, promotion, and progression.

Abbreviations: ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; NF-κB, nuclear factor kappa B; ECM, extracellular matrix.

The chemical profiles need careful classification to understand how these bioactive components act as protectants. To provide a foundation for these mechanisms, the next section systematically categorizes the major structural families of phytochemicals and considers their main dietary and medicinal sources.

Classification and Dietary Sources of Phytochemicals

1. Major Classes of Phytochemicals

Plant secondary metabolites are highly diverse in structure and require classification in a systematic manner, by their biosynthetic pathways and core chemical scaffolds. Of these polyphenols are the most abundant, containing one or more aromatic rings with hydroxyl groups. Flavonoids are one of the largest subclasses of polyphenols that share a flavan C_6-C_3-C_6 structure, such as epigallocatechin gallate (EGCG) and quercetin, with their exceptional chemopreventive properties mediated by modulation of cellular stress responses [7]. Non-flavonoid polyphenols include stilbenes, which include resveratrol, a compound that is widely studied in relation to its DNA stabilizing properties. The second prominent nitrogen containing basic compounds are the alkaloids, including berberine and piperine, which are involved in the interaction with intracellular targets to stop abnormal cell proliferation [8].

Beyond polyphenols and alkaloids, terpenoids constitute another major class of phytochemicals comprising monoterpenes, sesquiterpenes, and triterpenes derived from five-carbon isoprene units. Representative triterpenoids, such as ursolic acid, exhibit potent chemopreventive activities by modulating membrane-associated signalling pathways, suppressing abnormal cell proliferation, and promoting apoptosis in pre-neoplastic cells [9]. In addition to terpenoids, organosulfur compounds represent an important group of bioactive metabolites. Sulforaphane, diallyl trisulfide, and related allyl sulfur compounds from Allium and cruciferous vegetables act as electrophilic molecules that activate cellular detoxification pathways and enhance xenobiotic metabolism. Another distinct class comprises carotenoids, including lycopene and β-carotene, whose extended conjugated double-bond systems enable efficient quenching of singlet oxygen and other reactive oxygen species, thereby protecting cellular macromolecules from oxidative damage [10].

Table 1: Classification of Major Phytochemicals, Their Representative Bioactive Compounds, Principal Dietary Sources and General Biological Activities

Phytochemical Class	Representative Bioactive Compounds	Principal Dietary Sources	General Biological Activities Relevant to Cancer Prevention
Polyphenols	Resveratrol, Curcumin, Ellagic acid, Catechins	Berries, grapes, turmeric, pomegranate, green tea	Potent antioxidant activity, free radical scavenging, modulation of oxidative stress, anti-inflammatory effects, regulation of cellular signaling
Flavonoids	Quercetin, Epigallocatechin gallate (EGCG), Kaempferol, Luteolin, Apigenin	Citrus fruits, onions, apples, tea, berries, leafy vegetables	Antioxidant activity, inhibition of inflammation, cell cycle regulation, apoptosis induction, immune modulation
Alkaloids	Berberine, Piperine, Indole-3-carbinol*	Berberis species, black pepper, cruciferous vegetables*	Inhibition of abnormal cell proliferation, regulation of metabolic enzymes, enhancement of bioavailability of bioactive compounds, modulation of intracellular signaling
Terpenoids	Ursolic acid, Limonene, Ginsenosides, Oleanolic acid	Citrus fruits, medicinal herbs, ginseng, rosemary, basil	Anti-inflammatory activity, antioxidant defense, inhibition of tumor cell proliferation, promotion of apoptosis, modulation of lipid metabolism
Organosulfur Compounds	Sulforaphane, Diallyl trisulfide, Allyl isothiocyanate, Allicin	Broccoli, cabbage, Brussels sprouts, garlic, onion	Induction of phase II detoxification enzymes, antioxidant defense, anti-inflammatory activity, enhancement of xenobiotic metabolism, cellular protection
Carotenoids	Lycopene, β-Carotene, Lutein, Zeaxanthin, Astaxanthin	Tomatoes, carrots, pumpkin, spinach, sweet potato, papaya	Quenching of reactive oxygen species, protection against oxidative DNA damage, immune support, maintenance of cellular integrity

Abbreviation: EGCG, epigallocatechin gallate.

2. Dietary Sources and Representative Bioactive Compounds

The human metabolic pool is directly affected by the diversity of foods consumed, which in turn leads to diversity in the phytochemicals present in the diet. Fruits, especially citrus fruits and berries, are also good sources of anthocyanins, flavanones and ellagitannins. For example, when pomegranate is consumed, the punicalagins are converted to anti-inflammatory urolithins in the gastrointestinal tract by microflora [11]. Glucosinolates present in cruciferous vegetables, including broccoli, cabbage, and Brussels sprouts, are converted into biologically active isothiocyanates and indoles through the action of plant myrosinase following tissue disruption. However, thermal processing such as prolonged cooking can inactivate plant myrosinase, reducing this conversion. Under these conditions, gut microbiota-derived myrosinase-like enzymes can partially compensate by metabolising glucosinolates into bioactive compounds, although conversion efficiency varies considerably among individuals depending on microbial composition [11]. Organosulfur derivatives (OSDs) from allium vegetables (garlic and onions) are added to the diet as either water-soluble or lipid-soluble.

Aside from produce, herbs and spices are potent sources of certain bioactive compounds. The curcumin present in turmeric is a lipophilic polyphenol, whereas piperine, the principal bioactive constituent of black pepper, is a bioavailability-enhancing alkaloid that improves the intestinal absorption and systemic availability of several phytochemicals, including curcumin. In contrast, gingerols present in ginger are phenolic compounds belonging to the

broader class of polyphenols. Whole cereals contain special lipophilic and hydrophilic phenolic acids such as ferulic acid and alkylresorcinols, which are found in the outer bran layer. Legumes are rich in isoflavones in the diet, including genistein and daidzein, both of which have diphenolic structures that are similar to the endogenous mammalian estrogens. Additionally, some traditional medicinal plants, such as Camellia sinensis and Withania somnifera, provide specific secondary metabolites, such as green tea catechins and the steroidal lactones referred to as withanolides [12].

It is important to recognize that the concentrations of phytochemicals obtained through habitual dietary intake are generally much lower than those employed in *in vitro* and preclinical experimental studies. Consequently, although regular consumption of phytochemical-rich foods contributes to long-term cancer prevention, the pharmacological effects observed under experimental conditions may not always be directly achievable through di*et alo*ne. Factors such as food processing, bioavailability, metabolism, and inter-individual variability further influence systemic exposure to these bioactive compounds. The classification of phytochemicals and the key dietary and medicinal plants from which they are derived is shown in Figure 2.

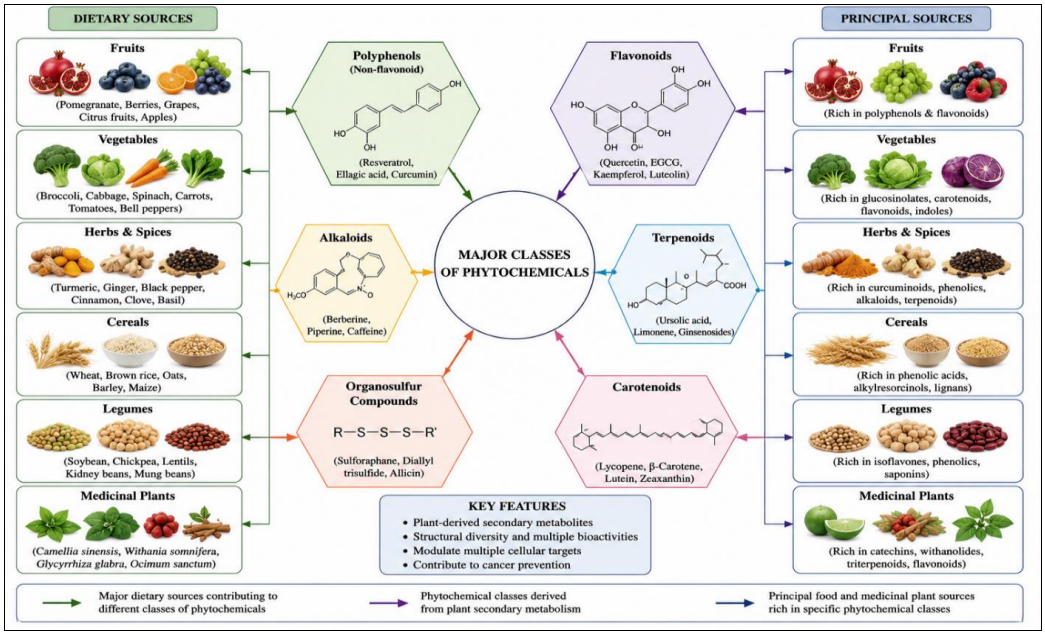

Fig 2: Classification of the major classes of phytochemicals together with representative dietary and medicinal plant sources associated with cancer chemoprevention. The figure illustrates the principal structural classes, including polyphenols, flavonoids, alkaloids, terpenoids, organosulfur compounds, and carotenoids, and highlights commonly consumed foods and medicinal plants that serve as natural sources of these bioactive compounds.

Abbreviations: EGCG, epigallocatechin gallate.

3. General Biological Activities Relevant to Cancer Prevention

Dietary phytochemicals have systemic preventive activity for oncogenic transformation based on their poly-functional biological activities. One of these is antioxidant activity, both directly and indirectly. The direct scavenging of reactive oxygen species (ROS) and reactive nitrogen species (RNS) with the donation of electrons or hydrogen atoms, affording protection of vital macro-molecules present in cells, such as genomic DNA, structural proteins and membrane lipids, from oxidative modification [13]. In an indirect way, these molecules also trigger the production of antioxidant enzymes in the body, increasing the intracellular presence of superoxide dismutase, catalase and glutathione peroxidase and maintaining the redox balance for long term.

At the same time, these compounds have potent anti-inflammatory effects that help to stop chronic inflammation, which is a key factor in the initiation of tumors. They inhibit excessive production of pro-inflammatory cytokines, chemokines and enzymes that generate eicosanoids, which leads to prevention of chronic tissue remodeling and oxidative stress. In addition, immunomodulatory activity is a crucial aspect of phytochemical activity: these compounds boost the host's immune system, enabling NK cells, macrophages, and CTLs to recognize and eliminate early immunogenic tumor cells before creating an immunogenic microenvironment [14]. Finally, these molecules offer protection to cells as they stimulate the induction of phase II detoxification enzymes, helping to metabolize and eliminate inert xenobiotics from the body before they can react with DNA and create DNA adducts that are mutagenic [15]. Collectively, these interconnected biological activities establish a multi-layered defence against carcinogenesis and provide the functional basis for the complex molecular signalling networks regulated by phytochemicals. Understanding how these biological effects are translated into specific intracellular signalling events is essential for elucidating their chemopreventive potential. Accordingly, the following section examines the principal molecular pathways through which phytochemicals regulate oxidative stress, inflammation, cell survival, apoptosis, epigenetic modifications, and tumour progression.

Molecular Mechanisms Underlying Cancer Prevention

1. Regulation of Oxidative Stress and Antioxidant Defense

Changes in the redox environment inside cells are the cause of carcinogenesis. In physiological conditions, the

controlled generation of ROS such as superoxide anions (O" "O" _2), hydrogen peroxide (H" "O" _2), and hydroxyl radicals (OH" "OH is an important mechanism for the regulation of intracellular signaling, cell proliferation, differentiation, and metabolic adaptation. These reactive species, however, if they are produced faster than their cellular antioxidant capacity, will cause long-lasting oxidative stress and thus damage important biological macromolecules. Lipid peroxidation occurs, membrane fluidity is altered and protein is oxidized by ROS. Importantly, the hydroxyl Radicals abstract hydrogen atoms from the deoxyribose sugars and purine or pyrimidine bases of DNA, causing both single- and double-strand breaks and formation of mutagenic base modifications like 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) [16]. Unrepaired genomic lesions give rise to transversion mutations during the process of genome replication, promoting proto-oncogene activation or tumor suppressor gene silencing and thus the initiation of tumorigenesis.

This initiation phase is interrupted by dietary phytochemicals, which reinforce the endogenous antioxidant networks. Enzymatic defense mechanism against reactive species: Transcriptional regulation of the expression of these primary antioxidant enzymes and phase II cytoprotective proteins, including heme oxygenase-1 (HO-1), is mediated by nuclear factor erythroid 2-related factor 2 (Nrf2) [17]. Cytoplasmically resident Nrf2 is normally poly-ubiquitinated and degraded by Kelch-like ECH-associated protein 1 (Keap1) via the ubiquitin-proteasome pathway. Bioactive phytochemicals containing electrophilic groups (such as sulforaphane, curcumin, resveratrol, epigallocatechin gallate (EGCG), and quercetin) bind to certain cysteine residues (Cys151, Cys273, Cys288) on Keap1. This modification prevents binding of Keap1-Nrf2, allowing newly synthesized Nrf2 to translocate to the nucleus, heterodimerize with small Maf proteins and bind antioxidant response elements (ARE) located in the promoter regions of cytoprotective genes. Increased expression of SOD, CAT, GPx and HO-1 restores redox homeostasis and maintains genomic integrity from oncogenic mutations.

2. Anti-Inflammatory Mechanisms

Chronic inflammation is a well-established characteristic of cancer and creates a conducive microenvironment for the promotion and progression of the disease. Recruitment of inflammatory cells continues to produce a stream of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) that work together to promote cell survival and tissue remodeling. A key mediator of this response is the nuclear factor kappa B (NF-κB) [18]. For when COX-2 is elevated, it promotes the conversion of arachidonic acid to prostaglandin E_2 (PGE_2) and through autocrine/paracrine signaling, it stimulates proliferation, inhibits apoptosis, promotes angiogenesis and facilitates the progression of tumors.

Oxidative stress and chronic inflammation are tightly interconnected through extensive biochemical crosstalk that sustains tumour initiation and progression. Elevated intracellular reactive oxygen species (ROS) activate IκB kinase (IKK), resulting in phosphorylation and degradation of IκB proteins, which permits the nuclear translocation of nuclear factor kappa B (NF-κB) and subsequent transcription of pro-inflammatory genes. Simultaneously, increased expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) promotes the excessive production of nitric oxide and superoxide radicals, leading to the formation of peroxynitrite ($ONOO^-$), a highly reactive oxidant that amplifies oxidative tissue injury and genomic instability. Importantly, Nrf2 and NF-κB signalling pathways exhibit reciprocal regulatory crosstalk, whereby activation of Nrf2 enhances antioxidant defence mechanisms, reduces intracellular ROS accumulation, and consequently suppresses ROS-dependent activation of NF-κB. Conversely, persistent NF-κB activation can attenuate Nrf2-mediated cytoprotective responses, thereby perpetuating chronic inflammation. Phytochemicals such as curcumin, epigallocatechin gallate (EGCG), and resveratrol disrupt this pathogenic cycle by inhibiting IKK activation, preventing NF-κB nuclear translocation, suppressing the expression of COX-2 and iNOS, and simultaneously activating Nrf2-dependent antioxidant pathways [19]. Through coordinated modulation of these interconnected signalling networks, phytochemicals restore redox homeostasis, attenuate chronic inflammatory cascades, and establish a cellular microenvironment that is less conducive to tumour initiation and pre-neoplastic progression.

3. Regulation of Cell Cycle, Apoptosis and Autophagy

Coordinated cell cycle progression and programmed cell death are both key components of tissue homeostasis, and often disrupted during malignant transformation. A series of cyclin-dependent kinase (CDK)/cyclin complexes (G_1/S, G_2/M) regulate the mammalian cell cycle. The pre-neoplastic cells escape checkpoints by overexpressing cyclins (Cyclin D1, Cyclin E) or by hyperactivating them (CDK4, CDK6, CDK2). Phytochemicals transcriptionally upregulate endogenous CDK inhibitors, such as p21 (CIP1/WAF1) and p27 (KIP1) that arrest cells in the cell cycle. Quercetin and EGCG increase the expression of p21 both in the p53-dependent and p53-independent manner, and they inhibit Cyclin D/CDK4/6 and Cyclin E/CDK2. This prevents the phosphorylation of retinoblastoma protein (Rb) and thus keeps the E2F transcription factor bound to inhibit entry into S phase for cell DNA repair or senescence [20].

Chemopreventative agents can take cells to the apoptotic pathway either through an extrinsic (receptor-mediated) pathway or an intrinsic (mitochondrial) pathway when the genetic damage is irreparable. The ratio of anti- vs pro-apoptotic proteins (Bcl-2/Bax, Bcl-X_L/Bak) controls the intrinsic pathway. Resveratrol, berberine and sulforaphane induce genotoxic stress which leads to conformational activation of Bax and down-regulation of Bcl-2. The apoptosome activates initiator caspase-9 which in turn activates executioner caspase-3 and caspase-7 to cleave substrates such as poly (ADP-ribose) polymerase (PARP) and finally causes DNA fragmentation [21]. At the same time, some phytochemicals upregulate death receptor (Fas and TRAIL) and initiator caspase-8, which activate the extrinsic pathway.

This cell death programme is coordinated with macroautophagy, a lysosome-mediated degradative process that exerts context-dependent effects during carcinogenesis. In the early stages of tumour development, autophagy functions predominantly as a tumour-suppressive mechanism by eliminating damaged organelles, misfolded

proteins, and genomically unstable cells, thereby maintaining cellular homeostasis and preventing malignant transformation. Conversely, in established tumours, autophagy may promote tumour cell survival by enabling adaptation to metabolic stress, hypoxia, nutrient deprivation, and anticancer therapies. Mechanistic target of rapamycin (mTOR) is a central negative regulator of autophagy, whereas Beclin-1 and lipidated LC3-II are essential mediators of autophagosome formation. Curcumin, epigallocatechin gallate (EGCG), and several other phytochemicals inhibit mTOR signalling, thereby promoting protective autophagy in early pre-neoplastic lesions through the removal of dysfunctional mitochondria and damaged proteins. Under conditions of sustained cellular stress or prolonged exposure, however, excessive activation of autophagy can act synergistically with apoptosis to induce irreversible tumour cell death, highlighting the dual and stage-dependent role of autophagy in cancer prevention and therapy.

4. Modulation of Epigenetic and Cellular Signaling Pathways

The epigenetic changes which accompany malignant transformation include regional hypermethylation of tumor suppressor genes, global hypomethylation of DNA and changes in histone modification patterns mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Non-coding microRNAs (miRNAs) also post-transcriptionally control by degrading mRNAs or by suppressing the translation of target mRNAs.

Nature, through the phytochemicals, is a natural epigenetic modulator ("epigenetic dietetics"). EGCG directly binds to and blocks catalytic pockets of DNA methyltransferases (DNMT1, DNMT3a, DNMT3b), which reverse hypermethylation of promoter CpG islands to restore expression of tumor suppressor genes like p16INK4a and PTEN. Sulforaphane competitively inhibits class I and II HDACs, thus promoting acetylation of histones H3 and H4 to unwind chromatin and facilitate the transcription of genes that regulate the cell cycle. At the same time, phytochemicals regulate miRNA expression, such as the downregulation of pro-survival transcripts via the upregulation of tumor-suppressive miR-34a and downregulation of oncogenic miR-21 by resveratrol [23].

Phytochemicals also act as regulators of mitogen-activated protein (MAPK) cascades, with their ability to inhibit hyper-activated Raf/MEK/ERK proliferation pathways and simultaneously to induce sustained phosphorylation of JNK and p38 to induce stress-induced apoptosis. Moreover, these agents are able to block canonical Wnt/β-catenin signaling. Without Wnt ligands, the destruction complex is responsible for directing the degradation of cytoplasmic β-catenin; binding of Wnt ligands to the receptor complex releases this destruction complex, allowing β-catenin to enter the nucleus and drive the transcription of c-Myc and Cyclin D1 through interaction with TCF/LEF. EGCG and curcumin prevent the destruction complex from getting destabilized and thus block the accumulation of β-catenin [24].

Phytochemicals also inhibit Janus kinase/signal transducer and activator of transcription (JAK/STAT3) signalling by suppressing JAK activation, thereby preventing STAT3 dimerisation and reducing the expression of survival-associated genes, including Bcl-xL and survivin. Importantly, these signalling pathways function as highly interconnected regulatory networks rather than isolated molecular cascades. Activation of Nrf2 reduces oxidative stress, thereby indirectly suppressing ROS-mediated activation of NF-κB, whereas inhibition of NF-κB further attenuates inflammatory signalling and oxidative damage. Similarly, suppression of the PI3K/Akt/mTOR pathway enhances apoptotic signalling while simultaneously promoting autophagy, and extensive crosstalk exists between PI3K/Akt, MAPK, p53, and Wnt/β-catenin pathways in regulating cell proliferation, DNA repair, and programmed cell death. Collectively, phytochemicals modulate these interconnected signalling networks to restore cellular homeostasis and suppress tumour initiation and progression. The principal molecular targets and signalling pathways regulated by representative phytochemicals are summarised in Table 2.

Table 2: Major Phytochemicals, Molecular Targets, Signaling Pathways, and Mechanisms Involved in Cancer Prevention

Phytochemical	Primary Molecular Target(s)	Major Signaling Pathway(s) Regulated	Mechanism(s) Contributing to Cancer Prevention
Curcumin	Keap1, IKK, COX-2, PI3K, Akt, mTOR, p53, HIF-1α, VEGF	Nrf2/ARE, NF-κB, PI3K/Akt/mTOR, MAPK, p53	Enhances antioxidant defense, suppresses inflammation, induces cell cycle arrest and apoptosis, promotes autophagy, inhibits angiogenesis and metastasis
Epigallocatechin gallate (EGCG)	Keap1, DNMTs, PI3K, β-catenin, IKK, COX-2, VEGF	Nrf2/ARE, NF-κB, PI3K/Akt, Wnt/β-catenin, MAPK	Reduces oxidative stress, inhibits inflammatory signaling, modulates epigenetic regulation, induces apoptosis, suppresses tumor progression
Resveratrol	SIRT1, NF-κB, STAT3, DNMTs, Bax/Bcl-2, p53, HIF-1α	SIRT1, NF-κB, JAK/STAT, p53, Nrf2, MAPK	Activates SIRT1-mediated cellular stress responses, restores redox homeostasis, suppresses chronic inflammation, promotes mitochondrial apoptosis, regulates microRNA expression, inhibits angiogenesis and enhances genomic stability.
Quercetin	PI3K, Akt, PTEN, Cyclin D/CDK4, CDK2, β-catenin	PI3K/Akt, MAPK, Wnt/β-catenin, p53	Induces G1/S cell cycle arrest, enhances apoptosis, inhibits proliferation, suppresses oxidative stress and inflammatory responses
Sulforaphane	Keap1, HDACs, Nrf2, MMP-2, MMP-9	Nrf2/ARE, NF-κB, Epigenetic regulation, EMT pathways	Activates antioxidant enzymes, inhibits histone deacetylases, suppresses invasion and metastasis, induces detoxification enzymes
Berberine	Bax/Bcl-2, Caspases, MMPs, AMPK	AMPK, MAPK, NF-κB	Promotes mitochondrial apoptosis, suppresses proliferation, inhibits extracellular matrix degradation and metastatic potential
Lycopene	ROS, IGF-1 signaling, VEGF	Antioxidant pathways, PI3K/Akt	Neutralizes reactive oxygen species, protects DNA integrity, inhibits angiogenesis and abnormal cell proliferation
β-Carotene	Reactive oxygen species, Nrf2	Nrf2/ARE	Scavenges free radicals, maintains cellular redox balance, protects against oxidative DNA damage

Indole-3-carbinol	Estrogen receptor, AhR, Cyclin-CDK complexes	AhR signaling, Cell cycle regulation, PI3K/Akt	Modulates estrogen metabolism, induces cell cycle arrest, promotes apoptosis and cellular differentiation
Piperine	NF-κB, STAT3, PI3K	NF-κB, JAK/STAT, PI3K/Akt	Suppresses inflammatory mediators, enhances apoptosis, improves bioavailability of co-administered phytochemicals
Ursolic Acid	mTOR, STAT3, VEGF, MMPs	PI3K/Akt/mTOR, JAK/STAT	Inhibits cell proliferation, angiogenesis, invasion, and metastatic progression

Abbreviations: Akt, protein kinase B; AhR, aryl hydrocarbon receptor; AMPK, AMP-activated protein kinase; ARE, antioxidant response element; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra-large; CAFs, cancer-associated fibroblasts; CDK, cyclin-dependent kinase; COX-2, cyclooxygenase-2; CTLs, cytotoxic T lymphocytes; DNMT, DNA methyltransferase; EGCG, epigallocatechin gallate; EMT, epithelial-to-mesenchymal transition; GPx, glutathione peroxidase; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor-1 alpha; HO-1, heme oxygenase-1; IKK, IκB kinase; JAK, Janus kinase; Keap1, Kelch-like ECH-associated protein 1; LC3, microtubule-associated protein 1 light chain 3; MAPK, mitogen-activated protein kinase; MDM2, mouse double minute 2 homolog; MMP, matrix metalloproteinase; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa B; NK, natural killer; Nrf2, nuclear factor erythroid 2-related factor 2; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; RNS, reactive nitrogen species; SIRT1, sirtuin 1; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TAMs, tumour-associated macrophages; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor.

The phytochemicals shown are representative examples of compounds that have been widely studied for their potential as cancer chemopreventives. They have pleiotropic effects, and multiple molecules, in some cases, typically act on several interconnected molecular targets and signaling pathways at the same time, thereby imparting multi-targeted chemopreventive activities.

5. Inhibition of Angiogenesis, Metastasis, and Immune Evasion

Pre-neoplastic lesions acquire the ability to support invasive growth, dissemination and escape host immune surveillance as they progress. Excessive levels of VEGF receptor tyrosine kinase binders promote capillary sprouting. The anti-HIF-1α effects of curcumin, EGCG and resveratrol include suppression of HIF-1α translation and stability, as well as inhibition of the binding of the VEGF receptor to HIF-1α (inhibition of endothelial migration and tube formation) [25].

To spread to distant sites, cells induce upregulation of the enzymes, called matrix metalloproteinases (MMP-2 and MMP-9), that break down structural type IV collagen in basement membranes. This invasive phenotype is promoted by epithelial-to-mesenchymal transition (EMT), which involves the loss of polarity and the decrease of E-cadherin adhesion in epithelial cells and the increase of N-cadherin adhesion and vimentin and Snail/Slug/Twist transcription factor in cells. Berberine, quercetin and sulforaphane are all inhibitors of MMP-2/9 activity and reverse EMT by increasing E-cadherin expression and decreasing Snail and Twist levels [26].

Cancer-associated fibroblasts (CAFs) in the tumour microenvironment (TME) transform normal fibroblasts into cells that remodel matrix architecture through transforming growth factor-beta (TGF-β). At the same time, the monocytes are polarized to secrete pro-tumorigenic tumour-associated macrophages (TAMs) with IL-10 and TGF-β. Phytochemicals disrupt this stromal remodeling, by blocking TGF-β signaling to prevent CAF activation and altering the TAM phenotype from tumour suppressive to antigen presenting.

Lastly these compounds combat immune evasion by enhancing the host immune surveillance. They enhance activation and cytotoxic activity of natural killer (NK) cells, cytotoxic T lymphocytes (CTLs) and dendritic cells. Additionally, there is emerging data that phytochemicals can inhibit programmed death-ligand 1 (PD-L1) upregulation on altered cells, thereby inhibiting the interaction between programmed death receptor 1 (PD-1) and programmed death-ligand 1 (PD-L1) that leads to T-cell exhaustion [27]. Dietary phytochemicals reduce tumour development in early stages by acting on four different levels: angiogenesis, tissue invasion, stromal remodeling and immune escape. Molecular signaling pathways that are likely to be involved in cancer initiation, promotion and progression and which are targeted by phytochemicals are shown in Figure 3.

Although the molecular mechanisms described in this section are supported by substantial experimental evidence, the majority of these findings originate from *in vitro* studies and animal models. The successful translation of these mechanistic observations into clinical practice remains limited because many phytochemicals exhibit poor bioavailability, rapid metabolism, low systemic exposure, and considerable inter-individual pharmacokinetic variability. Consequently, additional well-designed human clinical trials are required to validate these molecular mechanisms under physiological conditions and determine their true clinical relevance for cancer prevention.

Abbreviations: Akt, protein kinase B; ARE, antioxidant response element; COX-2, cyclooxygenase-2; EGCG, epigallocatechin gallate; HDAC, histone deacetylase; IKK, IκB kinase; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; VEGF, vascular endothelial growth factor; Wnt, Wingless/Integrated signalling pathway.

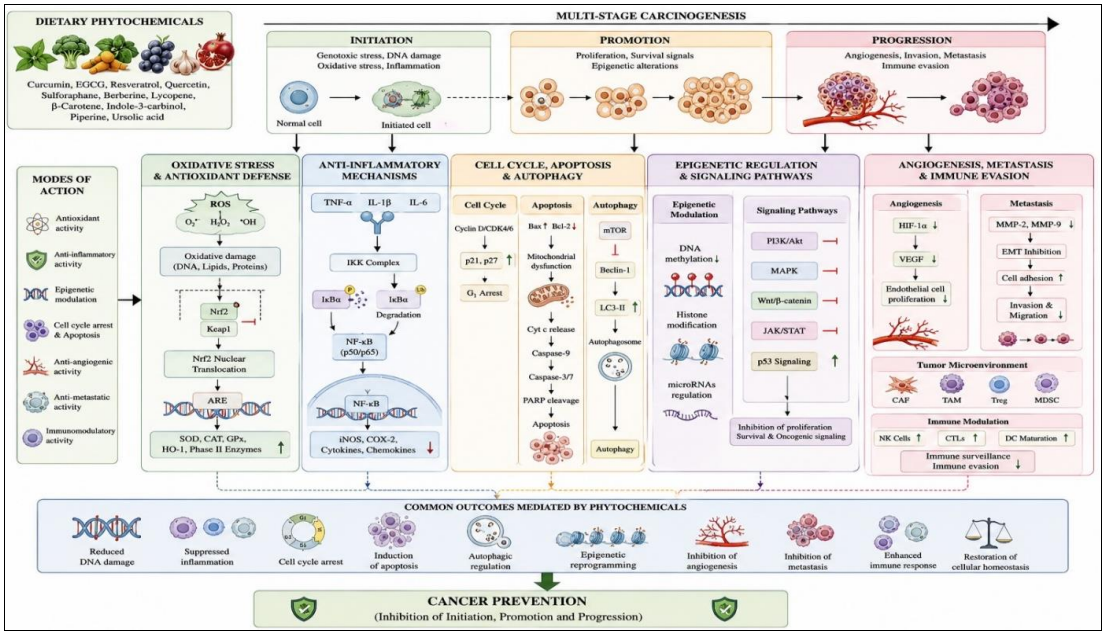

Fig 3: Integrated molecular signalling pathways modulated by phytochemicals during cancer initiation, promotion, and progression. Dietary phytochemicals regulate interconnected signalling networks involved in antioxidant defence, inflammation, cell cycle control, apoptosis, autophagy, epigenetic regulation, angiogenesis, metastasis, and immune evasion through coordinated modulation of multiple intracellular pathways.

Current Advances and Clinical Perspectives

1. Recent Experimental and Preclinical Advances

Reliability of phytochemicals as possible chemopreventive agents depends on a continuous research process that starts with the rigorous experimental model. *In vitro* studies continue to be the cornerstone for evaluating bioactive plant extracts, with a variety of immortalized pre-neoplastic and malignant human cell lines, such as the breast carcinoma cells (MCF-7, MDA-MB-231), the colorectal carcinoma cells (HCT116, HT-29), and prostatic neoplastic cells (PC-3). These cell-based systems have yielded strong support for the multi-targeted activity of a wide range of chemical classes. Consistently, phenolic compounds, terpenoids and alkaloids show a capacity to inhibit the uncontrolled proliferation of cells, to reset normal redox states, and to inhibit pro-inflammatory cascades as described above. Comparative *in vitro* studies suggest that certain compounds, e.g., EGCG and resveratrol, are very effective as single agents in specific models but, when used individually, are frequently administered at micromolar concentrations but not found to be safe physiologically.

Advanced animal models are used for preclinical validation to connect cell culture models and complex systemic physiology. Chemically induced carcinogenesis models are those including the azoxymethane/dextran sulfate sodium model of colorectal cancer, the 7,12-dimethylbenz [a]anthracene model of mammary tumorigenesis; genetically engineered mouse models include the Adenomatous Polyposis Coli (APC^(Min/+)) mouse. These *in vivo* models have shown that chronic feeding or systemic delivery of phytochemicals can effectively inhibit tumor initiation as well as subsequent clonal expansion during tumor promotion. Clinically this intervention results in a marked decrease in overall tumor incidence, in the absolute amount of tumor, in the number of macro pre-neoplastic lesions like aberrant crypt foci [28]. In addition, histopathological analyses validate the ability of these agents to inhibit the formation of new blood vessels in the microvasculature (angiogenesis) and to reduce the ability of blood vessels to break through the basement membrane (downregulation of metastatic enzymes). Importantly, in rats, this plant derived molecules do not lead to chronic or acute toxicity in the liver, kidney or the blood, further supporting their potential for chronic prophylactic use.

In addition to compounds known historically as phytochemicals, newer discovery approaches have led to the identification of new phytochemicals that have high chemopreventive potential. The dietary flavonols such as fisetin found in strawberries and naphthoquinones such as plumbagin in Plumbaginaceae have been shown to selectively induce elimination of senescent/pre-malignant cells and maintain the architecture of normal tissue, earning them scientific interest. At the same time, the development of multi-targeted natural product screening highlights the therapeutic potential of natural product combinations that have been designed. For example, the synergy between curcumin and piperine is clearly apparent in their mechanism of action, with the former acting as a temporary inhibitor of glucuronidation enzymes in the intestine to increase the amount of curcumin in target tissues. These well-orchestrated pre-clinical responses are the biological underpinning necessary to support the structural translation to the human clinical design.

2. Human studies and clinical evidence.

Strong preclinical evidence must ultimately be validated through well-designed human clinical trials and large-scale epidemiological investigations before definitive recommendations can be made for cancer prevention. During the past decade, numerous Phase I–III clinical trials have evaluated purified phytochemical formulations and standardized botanical extracts with respect to safety, tolerability, pharmacokinetics, and chemopreventive efficacy. Several studies have monitored surrogate biomarkers, including circulating inflammatory cytokines, oxidative stress markers, and tissue proliferation indices such as Ki-67, to evaluate biological responses. For example, standardized green tea extract (Polyphenon E)

demonstrated favourable safety profiles and significant reductions in disease-associated biomarkers among individuals with high-grade prostatic intraepithelial neoplasia (HGPIN) and oral leukoplakia [29]. Nevertheless, the promising efficacy observed in preclinical studies has not consistently translated into comparable clinical outcomes. This discrepancy is attributed to several pharmacological limitations, including poor aqueous solubility, limited gastrointestinal absorption, rapid first-pass metabolism and glucuronidation, chemical instability, low systemic bioavailability, and substantial inter-individual pharmacokinetic variability arising from genetic polymorphisms and differences in gut microbiota composition. Consequently, many phytochemicals fail to achieve therapeutically effective concentrations in human tissues despite demonstrating potent activity under experimental conditions.

A lot of epidemiological and population-based studies are also conducted to reflect these discrepancies. The relative risk of common epithelial malignancies (such as lung, gastric, and colorectal cancer) has been shown to have an inverse relationship with high consumption of dietary phytochemicals in long term prospective cohort and retrospective case control studies. Notably, the protective effects of the Mediterranean diet are shown in population-based data that this diet is a rich source of polyphenols, carotenoids, and organosulfur molecules. However, there are conflicting epidemiological reports, and the association of phytochemical intake with statistical significance is diminished after adjusting for other confounding lifestyle factors such as physical activity, smoking, and calorie consumption. Table 3 highlights representative preclinical and clinical studies published from 2018 to 2025, which reviewed the phytochemicals for cancer prevention.

Human clinical research has shifted to studies of controlled dietary interventions, to account for these differences. These protocols examine the physiological effects of whole-food diets, functional foods and specific nutraceutical supplementation, not of isolated synthetic compounds. Investigations using cruciferous vegetable concentrate (CVC) extracts and lycopene-rich functional food matrices have demonstrated that whole-food matrices frequently provide greater biological activity than equivalent amounts of isolated phytochemicals because of synergistic interactions among naturally occurring bioactive compounds. Current human evidence is strongest in terms of validating long-term safety and systemic tolerability of these dietary components. There are however several gaps in knowledge, such as lack of standardized dosing regimens, limited knowledge of long-term phase III survival data, and a lack of understanding of individual metabolic variations and their effect on clinical outcome.

3. Emerging Therapeutic Strategies

In the present cancer prevention research, several emerging technologies and translative approaches are used to overcome inconsistencies in the clinical history and to optimize the systemic application of plant-derived compounds. One of the major objectives of current translational research is the development of combination therapies in which phytochemicals are administered alongside conventional chemotherapy, targeted therapies, or immune checkpoint inhibitors to improve therapeutic efficacy while reducing treatment-associated toxicity.

Preclinical investigations have demonstrated encouraging synergy between several phytochemicals and immunotherapeutic agents. For example, curcumin has been shown to enhance anti-tumour immune responses and improve the efficacy of anti-PD-1/PD-L1 checkpoint blockade by reducing tumour-associated immunosuppression and inflammatory signalling, whereas resveratrol has been reported to modulate PD-L1 expression and improve T-cell-mediated immune responses in experimental cancer models. Similarly, EGCG and sulforaphane have demonstrated immunomodulatory effects capable of enhancing antigen presentation and reducing immune evasion in preclinical studies. Although these findings remain largely limited to experimental models, they provide a strong rationale for future clinical trials investigating phytochemical–immunotherapy combinations. The translational journey that moves from phytochemical discovery to the preclinical evaluation to the clinical application is outlined in Figure 4.

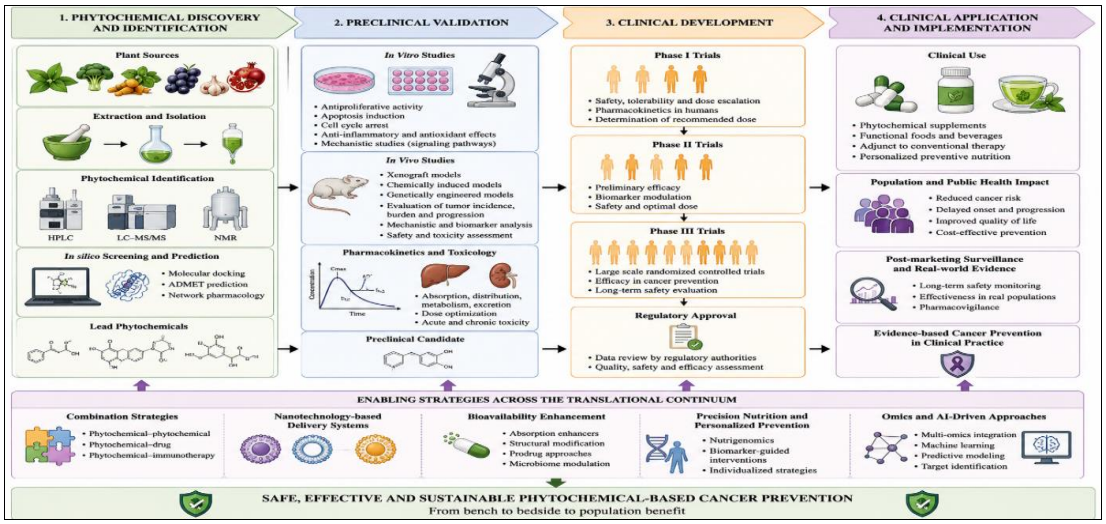

Fig 4: Translational pathway describing the progression of phytochemical-based cancer prevention strategies from compound discovery through mechanistic studies, preclinical validation, clinical evaluation, and eventual implementation in evidence-based precision oncology. The figure highlights the sequential stages required for successful clinical translation, including molecular target identification, pharmacokinetic optimisation, formulation development, biomarker validation, and clinical trials.

Abbreviations: AI, artificial intelligence; PK, pharmacokinetics; RCT, randomized controlled trial.

Table 3: Representative preclinical and clinical studies (2018–2025) evaluating phytochemicals in cancer prevention

Phytochemical / Intervention	Reference (Author, Year)	Clinical Trial / NCT Identifier	Study Phase / Design	Cancer Model / Population	Dose / Intervention	Major Findings	Primary Outcome / Statistical Endpoint	Clinical / Translational Significance
Curcumin	Anand *et al*., 2008	N/A	*In vitro*	Breast, colorectal, and prostate cancer cell lines	NR	Suppressed cell proliferation, induced apoptosis, inhibited NF-κB and PI3K/Akt signalling	Significant reduction in cell viability and increased apoptosis (NR)	Demonstrated potent multi-targeted chemopreventive activity and established the basis for translational studies.
Curcumin + Piperine	Shoba *et al*., 1998	N/A	Animal study	Chemically induced colorectal cancer model	NR	Improved curcumin bioavailability, reduced tumour incidence and inflammatory biomarkers	Enhanced bioavailability with reduced tumour burden (NR)	Demonstrated synergistic effects and highlighted the importance of bioavailability enhancement.
Epigallocatechin gallate (EGCG)	Yang *et al*., 2016	N/A	*In vitro*	Breast and colorectal cancer cell lines	NR	Reduced oxidative stress, inhibited cell cycle progression and promoted apoptosis	Reduced oxidative stress markers and increased apoptosis (NR)	Supported further development of green tea polyphenols for chemoprevention.
Sulforaphane	Clarke *et al*., 2011	N/A	Animal study	APCMin/+ mouse model	NR	Reduced intestinal polyp formation, activated Nrf2 signalling and suppressed inflammation	Reduced intestinal polyp number and inflammatory biomarkers (NR)	Validated antioxidant-mediated prevention of early tumorigenesis.
Resveratrol	Carter *et al*., 2014	N/A	Animal study	Breast and colon cancer models	NR	Inhibited angiogenesis and metastasis through suppression of VEGF and MMP expression	Reduced angiogenesis and metastatic markers (NR)	Demonstrated anti-metastatic and anti-angiogenic potential *in vivo*.
Fisetin	Yousefzadeh *et al*., 2018	N/A	Preclinical study	Multiple experimental tumour models	NR	Eliminated senescent cells, inhibited proliferation and promoted apoptosis	Reduced tumour growth and increased apoptosis (NR)	Emerging senolytic phytochemical with promising chemopreventive potential.
Plumbagin	Tripathi *et al*., 2019	N/A	Preclinical study	Experimental carcinoma models	NR	Suppressed tumour growth through oxidative stress modulation and apoptosis induction	Reduced tumour volume and oxidative stress biomarkers (NR)	Emerging phytochemical targeting multiple oncogenic pathways.
Standardized Green Tea Extract (Polyphenon E)	Bettuzzi *et al*., 2006	NR	Randomized Clinical Trial	Patients with high-grade prostatic intraepithelial neoplasia (HGPIN)	NR	Reduced disease progression biomarkers with good tolerability	Significant improvement in disease biomarkers with favourable safety profile	Supported the clinical feasibility of phytochemical-based cancer prevention.
Green Tea Polyphenols	Tsao *et al*., 2009	NR	Clinical Trial	Patients with oral leukoplakia	NR	Improved clinical response and reduced biomarkers associated with malignant transformation	Improved lesion response and biomarker reduction (NR)	Demonstrated preventive activity against precancerous lesions.
Mediterranean Diet (Phytochemical-rich Dietary Pattern)	Schwingshackl *et al*., 2017	N/A	Prospective Cohort Study	Large population cohorts	Long-term dietary adherence	Higher adherence associated with lower incidence of colorectal, gastric and several epithelial cancers	Reduced cancer incidence after multivariable adjustment (NR)	Reinforced the importance of long-term phytochemical-rich dietary patterns for cancer prevention.
Cruciferous Vegetable Concentrate (CVC) Intervention	Fahey *et al*., 2012	N/A	Dietary Intervention Study	High-risk populations	Dietary intervention	Increased isothiocyanate exposure, improved detoxification enzyme activity and reduced oxidative stress biomarkers	Increased Phase II detoxification activity and reduced oxidative stress biomarkers (NR)	Demonstrated the effectiveness of whole-food interventions over isolated phytochemicals.
Lycopene-rich Functional Foods	Graff *et al*., 2016	N/A	Dietary Intervention Study	Men at increased risk of prostate cancer	Dietary intervention	Reduced oxidative stress and improved prostate-related biomarkers	Improved prostate biomarkers and reduced oxidative stress (NR)	Supported dietary-based strategies for long-term cancer prevention.

Nano technology delivery systems are a big challenge to clinical translation of these molecules. The most active phytochemicals have great pharmacological shortcomings such as low aqueous solubility, low gastrointestinal absorption, high rate of first-pass hepatic metabolism, and rapid systemic elimination that limit their bioavailability. To overcome these problems, delivery systems such as biodegradable polymeric nanoparticles, liposomes, solid lipid nanoparticles and nanoemulsions have been created to be able to encapsulate such hydrophobic compounds [30]. All these nanoformulations, which enhance the aqueous solubility, shield the active compounds from premature enzymatic degradation in the gastrointestinal tract, prolong systemic circulation time and enable targeted sustained release in peripheral target tissues, increase the overall chemopreventive activity.

At the same time, the field is moving towards precision nutrition and personalised cancer prevention based on nutrigenomics and nutrigenetics of the diet. It's a paradigm that accounts for the fact that there are individual genetic differences such as single nucleotide polymorphisms in phase II detoxification genes or antioxidant enzyme sequences which determine the way in which a person metabolises and responds to certain dietary components. Moreover, gut microbiome is a complex community that significantly influences the bioavailability and metabolism of complex plant molecules, such as the microbial conversion of ellagitannins to urolithins. Combining multi-omic profiling and dietary intervention with biomarkers will enable the creation of a personalized preventive nutrition strategy specific to a person's biological makeup and gut microbiome. A combination of these combined pharmacological and technological innovations is bringing plant-based compounds closer to precision cancer prevention via evidence-based approaches.

Challenges, Limitations, And Future Perspectives

1. Current Challenges and Limitations

Although there is persuasive preclinical data showing the multi-target chemopreventive potential of plant secondary metabolites, the successful implementation of these results into clinical practice in oncology is hindered by a number of formidable both pharmacological and regulatory challenges. The bioavailability of most phytochemicals remains one of the principal barriers to successful clinical translation. Hydrophobic compounds such as curcumin and resveratrol exhibit poor aqueous solubility, limiting gastrointestinal dissolution and intestinal absorption. Following oral administration, these compounds undergo extensive first-pass metabolism in both enterocytes and hepatocytes, where they are rapidly transformed through Phase II conjugation reactions, including glucuronidation, sulfation, and methylation. Although these metabolic processes facilitate elimination, they frequently generate conjugated metabolites with substantially lower biological activity than their parent compounds, thereby reducing systemic exposure to pharmacologically active forms. Consequently, plasma and tissue concentrations achieved following dietary intake or conventional oral supplementation are often considerably lower than those required to reproduce the therapeutic effects observed in experimental models [31].

This is complicated by the fact that these bioactive molecules are chemically unstable. Many phytochemicals are very sensitive to the physiological pH changes and are oxidized or undergo enzymatic hydrolysis at high rate in the harsh and fluctuating environment of gastrointestinal tract, before they are absorbed into the systemic circulation [32]. Furthermore, they are prone to thermal and photo-degradation, which is a serious challenge for the long-term storage and shelf-life optimization of pharmaceuticals.

These pharmacological constraints are complicated by serious standardization problems, associated with non-reproducible clinical results. The biochemical composition of the extracts from the plants varies widely and depends on the species of plants, the cultivar, geographic origin and seasonal environmental variations. Commercial formulations are often not standardized, due to the variability in extraction methods, processing methods, and the absence of strict quality control parameters, which can lead to different amounts of the target bioactives [33]. Therefore, this batch-to-batch variation can make it very difficult to reproduce the results of clinical trials or to identify an optimal dose.

In addition, human translation is complicated because of the variability of internal pharmacokinetics of individuals. Gastrointestinal transit time, different expression of metabolic enzymes, and different gut microbiota composition of humans and animals have a significant impact on the bioactivation and absorption of these complex plant molecules. Genetic polymorphisms in phase I cytochrome P450 enzymes or phase II conjugating transferases change individual metabolism, and concomitant drug–phytochemical interactions can result in unpredictable changes in the systemic clearance of both the phytochemical and co-administered conventional drugs.

Such variations require a re-evaluation of the safety and toxicity profile. But while it is often assumed that plants are naturally occurring and thus cannot be harmful, many phytochemicals are shown to have dose-dependent toxicities and off-target side effects when consumed in purified, high-dose nutraceutical form. Herb–drug interactions can be severe, especially because they competitively inhibit metabolic enzymes or efflux transporters, such as P-glycoprotein, leading to regulatory concerns about their long-term safety in patient populations.

Lastly, there is a lack in clinical validation of the field. Most of the completed human studies have small sample sizes, short follow-up times, heterogeneous study designs, and use surrogate biochemical endpoints instead of clinically meaningful endpoints such as long-term cancer incidence or overall survival rates. Clearing the remaining gaps in pharmacology, standardization, and clinical utility requires these secondary plant metabolites to make the leap from bench to bedside to become validated and evidence-based preventive oncology tools.

2. Future Perspectives

Current research is increasingly integrating advanced technological approaches to overcome the pharmacological limitations associated with phytochemicals. Nanotechnology-based delivery systems, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, and stimuli-responsive nanocarriers, have demonstrated considerable potential to improve aqueous solubility, gastrointestinal stability, controlled drug release, and tissue-specific delivery, thereby enhancing systemic bioavailability and therapeutic efficacy. Nevertheless, nanomedicine should not be regarded as a universal

solution. Important challenges remain regarding long-term nanoparticle toxicity, immunogenicity, large-scale manufacturing, production costs, formulation reproducibility, regulatory approval, and clinical scalability. Addressing these issues will be essential before nanoformulations can be routinely incorporated into evidence-based cancer prevention strategies.

High-throughput multi-omics technologies are transforming the understanding of phytochemical pharmacodynamics by integrating genomics, transcriptomics, proteomics, metabolomics, epigenomics, and microbiome profiling into a unified systems biology framework. Rather than examining isolated molecular events, these complementary approaches enable comprehensive mapping of cellular signalling networks regulated by phytochemicals, facilitate the discovery of predictive biomarkers, identify responder populations, and improve understanding of individual variability in metabolism and therapeutic response. Such systems-level analyses provide an important foundation for precision cancer prevention and biomarker-guided clinical interventions.

Artificial intelligence (AI) is increasingly complementing multi-omics approaches by accelerating phytochemical discovery and translational research. Machine learning algorithms, network pharmacology, molecular docking, and virtual high-throughput screening facilitate the identification of novel molecular targets, prediction of phytochemical–protein interactions, optimisation of lead compounds, and modelling of pharmacokinetic and toxicity profiles before experimental validation [38]. Integrating AI with multi-omics datasets offers a powerful framework for identifying synergistic phytochemical combinations, improving precision nutrition strategies, and supporting the rational design of future clinical trials.

These computational and omic discoveries intersect directly to precision oncology and personalized cancer prevention. Rather than a "one size fits all" dietary recommendation, “personalised” preventive medicine utilises the findings of nutrigenomics and pharmacogenomics to design specific phytochemical interventions that are aimed at an individual's specific genetic make-up, metabolic potential and individual risk profile. Specific genetic polymorphisms of antioxidant or detoxification pathways can be used to create biomarker-driven, personalized preventive nutrition strategies that optimize individual protective responses. The main obstacles to the clinical translation of phytochemicals, along with new opportunities and future research areas, are summarized in Figure 5.

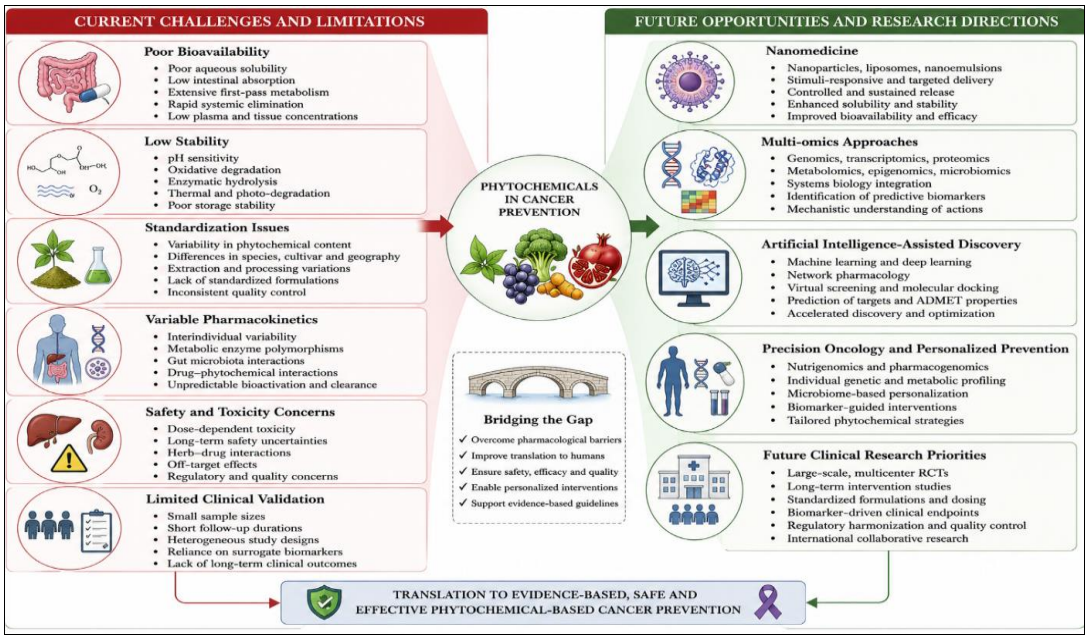

Fig 5: Current challenges, emerging opportunities, and future directions for the clinical translation of phytochemical-based cancer prevention. The figure summarises the major barriers limiting clinical implementation, including poor bioavailability, first-pass metabolism, Phase II conjugation, formulation variability, and insufficient clinical validation, together with emerging solutions such as nanotechnology-based drug delivery, biomarker-guided precision nutrition, multi-omics integration, artificial intelligence-assisted drug discovery, and standardized multicentre clinical trials.

Abbreviations: AI, artificial intelligence; PK, pharmacokinetics; RCT, randomized controlled trial.

Realising the full clinical potential of phytochemicals will require coordinated efforts across basic, translational, and clinical research. Future priorities should include large-scale multicentre randomised controlled trials with harmonised study designs, validated biomarker-driven endpoints, standardised phytochemical formulations, and robust pharmacokinetic evaluation to establish optimal dosing strategies and long-term safety profiles. In parallel, advances in nanotechnology, artificial intelligence, systems biology, and precision nutrition should be integrated into well-designed clinical research programmes while addressing regulatory, manufacturing, and scalability challenges. Through sustained interdisciplinary collaboration among molecular biologists, pharmacologists, oncologists, nutrition scientists, nanotechnologists, bioinformaticians, and regulatory agencies, phytochemical research can progress from promising experimental observations toward evidence-based, clinically validated precision cancer prevention strategies that are both scientifically rigorous and broadly applicable.

Conclusion

The comprehensive evaluation of phytochemicals presented in this review highlights their considerable potential as multi-targeted chemopreventive agents capable of interfering with multiple stages of carcinogenesis. Preclinical and experimental evidence demonstrates that these structurally diverse plant-derived secondary metabolites modulate a broad spectrum of intracellular signalling pathways by restoring redox homeostasis through Nrf2 activation, suppressing chronic inflammation via inhibition of NF-κB and COX-2 signalling, enforcing cell cycle checkpoints, inducing apoptosis and cytotoxic autophagy, regulating epigenetic modifications, and inhibiting angiogenesis, invasion, and immune evasion. Collectively, these pleiotropic mechanisms suggest that phytochemicals offer complementary multi-target therapeutic potential that may enhance existing cancer prevention and treatment strategies, rather than replacing conventional single-target therapies.

Despite these promising findings, the successful clinical translation of phytochemicals remains constrained by several important challenges, including poor aqueous solubility, limited systemic bioavailability, chemical instability, lack of standardized formulations, considerable inter-individual pharmacokinetic variability associated with genetic polymorphisms and gut microbiota composition, and the limited availability of large-scale, long-term, multicentre Phase III clinical trials. Emerging advances in nanotechnology-based delivery systems, multi-omics profiling, artificial intelligence-driven network pharmacology, and biomarker-guided precision nutrition provide promising opportunities to overcome these barriers and improve the clinical applicability of phytochemical-based interventions.

Future progress will depend on rigorous interdisciplinary collaboration among molecular biologists, pharmacologists, oncologists, nutrition scientists, nanotechnologists, bioinformaticians, and computational researchers to establish standardized formulations, optimize dosing strategies, identify predictive biomarkers, and generate high-quality clinical evidence. With continued technological innovation and robust clinical validation, dietary phytochemicals have the potential to become scientifically validated components of evidence-based precision cancer prevention, contributing to more effective, personalized, and sustainable public health strategies.

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